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Multi-ancestry genome-wide gene-sleep interactions identify novel loci for blood pressure

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Multi-ancestry genome-wide gene-sleep interactions identify novel loci for blood pressure

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Abstract

Long and short sleep duration are associated with elevated blood pressure (BP), possibly through effects on molecular pathways that influence neuroendocrine and vascular systems. To gain new insights into the genetic basis of sleep-related BP variation, we performed genome-wide gene by short or long sleep duration interaction analyses on four BP traits (systolic BP, diastolic BP, mean arterial pressure, and pulse pressure) across five ancestry groups in two stages using 2 degree of freedom (df) joint test followed by 1df test of interaction effects. Primary multi-ancestry analyses in 62,969 individuals in stage 1 identified 3 novel gene by sleep interactions that were replicated in an additional 59,296 individuals in stage 2 (stage 1+2 $P_{\text{joint}} < 5 \times 10^{-8}$), including rs7955964 (*FIGNL2/ANKRD33*) that increases BP among long sleepers, and rs73493041 (*SNORA26/C9orf170*) and rs10406644 (*KCTD15/LSM14A*) that increase BP among short sleepers ($P_{\text{int}} < 5 \times 10^{-8}$). Secondary ancestry-specific analyses identified another novel gene by long sleep interaction at rs111887471 (*TRPC3/KIAA1109*) in individuals of African ancestry ($P_{\text{int}} = 2 \times 10^{-6}$). Combined stage 1 and 2 analyses additionally identified significant gene by long sleep interactions at 10 loci including *MKLNI* and *RGL3/ELAVL3* previously associated with BP, and significant gene by short sleep interactions at 10 loci including C2orf43 previously associated with BP ($P_{\text{int}} < 10^{-3}$). 2df test also identified novel loci for BP after modeling sleep that have known functions in sleep-wake regulation, nervous and cardiometabolic systems. This study indicates that sleep and primary mechanisms regulating BP may interact to elevate BP level, suggesting novel insights into sleep-related BP regulation.

Introduction

Hypertension (HTN), including elevations in systolic blood pressure (SBP) and/or diastolic blood pressure (DBP), is a major risk factor for cardiovascular diseases, stroke, renal failure and heart failure¹. The heritability of HTN is estimated to be 30-60% in family studies^{2,3}. Recent well-powered large genome-wide association studies (GWAS) of blood pressure (BP) have identified over 1,000 loci; however, in total these explain less than 3.5% of BP variation⁴⁻¹⁶. As complex traits are the likely result of an interplay between genes and the environment, gene-environment (G×E) interaction analyses have been proposed as a promising approach to explain additional heritability and identified novel loci for traits associated with cardiometabolic diseases^{17,18}.

Long and short sleep durations are associated with elevated BP, possibly through effects on molecular pathways that influence neuroendocrine and vascular systems¹⁹. Recent multi-ancestry interaction analyses between genetic variants and sleep duration (gene-sleep for short) on blood lipid traits have identified novel loci and potentially distinct mechanisms for short- and long-sleep associated dyslipidemia, and suggest a modification effect of sleep-wake exposures on lipid biology¹⁸. We hypothesize that differences in sleep duration may also modify the effect of genetic factors on BP. Genome-wide interaction study (GWIS) accounting for potential gene-sleep interactions may help identify novel BP loci and reveal new biological mechanisms that can be explored for treatment or prevention of HTN.

Within the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Gene-Lifestyle Interactions Working Group²⁰, we investigate gene-sleep interactions on BP traits in 122,265 individuals from five ancestry groups. We perform GWIS using 2df joint test of main and interaction effects²¹ followed by 1df test of interaction effect to identify novel gene-

sleep interactions and gene-BP associations accounting for sleep duration.

Materials and methods

We performed genome-wide meta-analysis of gene-sleep interactions on four BP traits (SBP, DBP, mean arterial pressure [MAP], and pulse pressure [PP]) in 30 cohorts of five ancestry groups in two stages (Supplementary Notes). Stage 1 discovery analyses included 62,969 individuals of European (EUR), African (AFR), Asian (ASN), Hispanic (HIS), and Brazilian (BRZ) ancestries from 16 studies (Supplementary Tables 1-3). Stage 2 replication analyses included 59,296 individuals of EUR, AFR, ASN and HIS ancestries from 14 additional studies (Supplementary Tables 4-6). We examined long total sleep time (LTST) and short total sleep time (STST) separately as lifestyle exposures. Given the heterogeneity of age, sleep duration and BP levels across cohorts and ancestry groups, as well as differences in how sleep duration was assessed (Supplementary Tables 2 and 5), we followed procedures used in prior research¹⁸ to categorize 20% of each sample as long sleepers and 20% as short sleepers based on responses to questionnaires, accounting for age and sex variability within each cohort (Supplementary Methods).

The overall study design is described in Fig. 1. To screen for both gene-sleep interactions and genetic main effect on BP accounting for sleep duration, we performed GWIS using 2df joint test of main and interaction effects adjusting for age, sex, population structure, and other cohort-specific covariates in each ancestry of each cohort using various software such as ProbABEL²², MMAP and R package sandwich²³ (Supplementary Table 3). Since BMI is associated with both sleep and BP^{24,25}, we performed another GWIS additionally adjusted for BMI to identify genetic loci through biological pathways independent of obesity. We then conducted 2 df joint fixed-

effects meta-analysis of the combined main and interaction effects (P_{joint}) using Manning et al's method implemented in the METAL software²¹ across multi-ancestry in stage 1 and stage 2 separately. Secondary ancestry-specific meta-analyses were performed restricted to EUR and AFR groups. We performed extensive study-level and meta-level quality controls (QCs) using the R package EasyQC²⁶ as described in Supplementary Methods.

Genetic variants with $P_{\text{joint}} < 10^{-6}$ in stage 1 were followed up in stage 2 replication analyses and subsequently meta-analyzed with stage 1 summary statistics. The replication significance threshold was defined as stage 2 $P_{\text{joint}} < 0.05$ and stage 1 + 2 $P_{\text{joint}} < 5 \times 10^{-8}$, with consistent directions of association effects. To maximize the statistical power, we also performed genome-wide combined stage 1 and 2 meta-analyses in multi-ancestry and EUR groups using a stricter significant threshold ($P_{\text{joint}} < 3.125 \times 10^{-9}$), after Bonferroni correction for two independent BP traits, two exposures, with and without BMI adjustment, in two groups.

We then investigate the interaction effect with sleep for the significant novel ($r^2 < 0.1$ and $> 1\text{Mb}$ from any previously identified BP locus) and known BP loci ($\leq 1\text{Mb}$) using 1df test (P_{int}). Novel gene-sleep interactions were identified with stage 1+2 $P_{\text{int}} < 10^{-3}$ accounting for the number of independent loci. We compared the risk effects on BP of loci significantly interact with sleep in individuals with LTST, STST, and normal sleep duration (60% of the sample; Supplementary Methods). The variance of four BP traits explained by the SNP main and interaction effects were estimated using summary statistics in combined analyses using the R package VarExp²⁷.

Significant novel loci were followed up for bioinformatics analyses. We annotated functional effects for the novel loci using HaploReg²⁸, Regulome²⁹, and GTex (v8)³⁰ database. Genes under the association regions were mapped using PLINK 2.0³¹ and SNPsea³² software and

were interrogated for associated phenotypes, Mendelian diseases, and druggable targets using PheGeni³³, OMIM³⁴, and DGIdb³⁵ database. Tissue and pathway enrichment analyses were performed using online software FUMA³⁶.

This work was approved by the Institutional Review Board of Washington University in St. Louis and complies with all relevant ethical regulations. For each of the participating cohorts, the appropriate ethics review board approved the data collection and all participants provided informed consent. All summary results are available in dbGaP (phs000930.v1.p1).

Code availability

The URLs of genetic software and database used in this study are provided as follows: ProbABEL, <https://github.com/GenABEL-Project/ProbABEL>; MMAP, <https://mmmap.github.io>; sandwich, <https://github.com/cran/sandwich>; METAL, <http://csg.sph.umich.edu/abecasis/metal/>; EasyQC, <http://www.genepi-regensburg.de/easyqc>; varExp, <https://github.com/vincela/VarExp>; HaploReg, <https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php>; RegulomeDB, <http://www.regulomedb.org/>; GTEx, <https://gtexportal.org/home/>; PLINK 2.0, <https://www.cog-genomics.org/plink/2.0/>; SNPsea, <http://pubs.broadinstitute.org/mpg/snpsea/>; PheGeni, <https://www.ncbi.nlm.nih.gov/gap/phegeni>; OMIM, <https://www.omim.org>; DGIdb, <https://www.dgidb.org>; FUMA, <https://fuma.ctglab.nl>. The detailed settings are described in Supplementary Methods.

Results

GWIS

The Miami and QQ plots of stage 1 2df GWIS in multi-ancestry, EUR and AFR groups are provided in Supplementary Figs 1-6. 1,976 genetic variants with $P_{\text{joint}} < 10^{-6}$ were followed up

for replication analyses. Of these, 1,081 variants were available in stage 2 cohorts and passed quality control, of which 268 (24.8%) variants showed $P_{\text{joint}} < 0.05$.

Our primary two-stage analyses in the multi-ancestry group formally replicated one novel locus (*FIGNL2/ANKRD33*; Table 1) and eight known loci (*ULK4*, *CHIC2*, *PRDM8/FGF5*, *IGFBP1/IGFBP3*, *PIK3CG*, *PDPI/CDH17*, *GPR20* and *ADAMTS8*; Supplementary Table 7) in 2df gene-LTST interaction analyses, and two novel loci (*SNORA26/C9orf170* and *KCTD15/LSM14A*; Table 1) and eight known loci (*ULK4*, *CHIC2*, *PRDM8/FGF5*, *IGFBP1/IGFBP3*, *PIK3CG*, *PDPI/CDH17*, *ADAMTS8* and *SH2B3*, Supplementary Table 7) in 2df gene-STST interaction analyses (stage 2 $P_{\text{joint}} < 0.05$ and stage 1 + 2 $P_{\text{joint}} < 5 \times 10^{-8}$). The regional association plots are shown in Supplementary Fig. 7.

In secondary ancestry-specific two-stage analyses, we formally replicated one known BP locus (*INSR*) in 2df gene-STST interaction analyses restricted to EUR individuals (stage 2 $P_{\text{joint}} < 0.05$ and stage 1 + 2 $P_{\text{joint}} < 5 \times 10^{-8}$; Supplementary Table 7). We additionally identified three novel loci (*TRPC3/KIAA1109*, *ANK*, and *RP11-322L20.1/RP11-736P16.1*) in 2df gene-LTST interaction analyses restricted to AFR individuals (stage 1 $P_{\text{joint}} < 5 \times 10^{-8}$ and stage 2 $P_{\text{joint}} < 0.05$, with consistent directions of main effects; Supplementary Table 8). The regional association plots are shown in Supplementary Fig. 8. However, these three variants did not survive our formal replication criteria of stage 1+2 $P_{\text{joint}} < 5 \times 10^{-8}$, possibly reflecting heterogeneity between discovery and replication cohorts.

Genome-wide combined stage 1 and stage 2 meta-analyses (Miami and QQ plots in Supplementary Figs 9-12) additionally identified 9 novel and 4 known BP loci in 2df gene-LTST interaction analyses; and 11 novel and 3 known BP loci in 2df gene-STST interaction analysis ($P_{\text{joint}} < 3.125 \times 10^{-9}$; Supplementary Tables 9 and 10). The regional association plots of the 20

novel loci are shown in Supplementary Fig. 13. Replication in independent datasets is needed to validate these unreported loci. Additional loci that were genome-wide significant ($3.125 \times 10^{-9} < P_{\text{joint}} < 5 \times 10^{-8}$) are also summarized in Supplementary Tables 11 and 12.

Interactions with sleep

We then investigated the 1df gene-sleep interaction effects of the 26 novel and 18 known loci identified in the two-stage or combined analyses. Among the formally replicated loci in multi-ancestry two-stage analyses, one novel locus rs7955964 (*FIGNL2/ANKRD33*) showed a genome-wide significant 1df SNP \times LTST interaction (stage 1+2 $P_{\text{int}} < 5 \times 10^{-8}$; Table 1) with risk effect on BP only present in long sleepers (Fig. 2A). Two novel loci, rs73493041 (*SNORA26/C9orf170*) and rs10406644 (*KCTD15/LSM14A*), showed genome-wide significant 1df SNP \times STST interactions (stage 1+2 $P_{\text{int}} < 5 \times 10^{-8}$; Table 1) with risk effects on BP only present in short sleepers (Fig 2B and C). Those effects were largely consistent across cohorts. In the EUR population, the aggregate main effects of these three loci explained up to 0.016% of the variation of four BP traits, while the gene-LTST and -STST interaction effects additionally explained 0.002-0.01% and 0.005-0.027% of the variation (Supplementary Table 13). In the AFR population, the aggregate main effect of these three loci explained 0.116-0.188% of the variation of four BP traits, while the gene-LTST and -STST interaction effects additionally explained 0.375-0.784% and 0.162-0.254% of the variation (Supplementary Table 13). Given the limited sample sizes in the AFR group, the estimation of BP variation in AFR is likely inflated.

In the two-stage analyses restricted to AFR individuals, one novel loci rs111887471 (*TRPC3/KIAA1109*) showed significant 1df SNP \times LTST interaction with risk effect on BP only

present in long sleepers (stage 1+2 $P_{\text{int}}=2\times 10^{-6}$; Supplementary Table 8 and Supplementary Fig 14A).

Among the loci identified in combined stage 1 and stage 2 analyses, eight novel loci (*LINC01720/AL138927.1*, *RYR2*, *SEMA4F/HK2*, *DPP10/DDX18*, *PDZRN3/CNTN3*, *LEKRI/LINC00880*, *FSTL5*, *AC008558.1/HTR1A*, and *ZFPM2*; Supplementary Table 9) and two previously reported BP loci (*MKLNI* and *RGL3/ELAVL3*; Supplementary Table 10) showed significant 1df interactions with LTST ($P_{\text{int}} < 1\times 10^{-3}$). The risk effects on BP in long sleepers differed from the effects in normal or short sleepers (Supplementary Fig 14A). Nine novel loci (*GJA4*, *PSRC1/MYBPHL*, *AL033381.3/FOXQ1*, *PTPRN2*, *ERICH1*, *AL162384.1/IL33*, *FRMD4A*, *RP11-408B11.2*, and *TTC6*; Supplementary Table 9) and one previously reported BP locus (*C2orf43*; Supplementary Table 10) showed significant 1df interactions with STST ($P_{\text{int}} < 10^{-3}$; Supplementary Table 9-10). The risk effects on BP in short sleepers differed from the effects in normal or long sleepers (Supplementary Fig 14B).

We also looked up the previously validated 362 BP loci⁴⁻¹⁵ and 113 sleep duration loci³⁷ in the combined analyses, but none of these showed significant 1df interactions after accounting for multiple comparisons ($P_{\text{int}} > 10^{-4}$; Supplementary Tables 14-17).

Associations with other relevant traits

2df two-stage and combined analyses total identified 26 novel loci for BP with or without significant 1df interactions (3 formally replicated in multi-ancestry two-stage analyses, 3 in AFR two-stage analyses, and 20 in combined analyses). We looked up the associations between those loci with cardiovascular diseases, stroke, chronic kidney disease, and self-reported and objective (derived from 7-day accelerometry) sleep traits using publicly available genome-wide summary statistics from large GWAS (Supplementary Tables 18-23). One of the replicated loci

rs73493041 (*SNORA26/C9orf170*) was associated with self-reported chronotype (morningness vs eveningness) ($P=9.1\times 10^{-6}$; Supplementary Table 22). Among the other novel loci, rs17036094 (*PSRC1/MYBPHL*) was associated with coronary artery disease and myocardial infarction ($P\leq 0.005$; Supplementary Table 19), and rs140526840 (*FSTL5*) was associated with chronic kidney disease ($P=0.006$; Supplementary Table 21),

Bioinformatics analyses

All of the 26 novel variants were mapped to intergenic or intronic regions using HaploReg²⁸, including 4 in promoter histone marks, 11 in enhancer histone marks, 10 in DNase, 3 altered the binding sites of regulatory proteins and 2 conserved elements (Supplementary Table 24).

Among the 3 replicated novel loci, rs73493041 (*SNORA26/C9orf170*) was an eQTL for *GAS1* in suprapubic skin using GTEx (v8)³⁰ (Supplementary Table 25). Using PLINK pruning and SNPsea³², rs7955964 (*SNORA26/C9orf170*) was mapped to a region of 10 genes (Supplementary Table 26), including *ANKRD33* and *NR4A1*, implicated in sleep-wake control regulation and the neurovascular system^{38,39}. Rs10406644 (*KCTD15/LSM14A*) was mapped to a region overlapping with 9 genes (Supplementary Table 27), including *KCTD15* and *CHST8*, previously associated with adiposity traits and involved in neurodevelopmental and neuropsychiatric diseases⁴⁰⁻⁴² (see Discussion).

Among the other 23 novel loci, 4 variants showed strong eQTL evidence across various tissues such as blood and adipose tissue (Supplementary Table 25). 14 loci were mapped to genes with known functions in cardiac and nervous systems (e.g., *TRPC3*⁴³, *RYR2*⁴⁴, *ANK2*⁴⁵, *GJA4*⁴⁶ and *SORT1*⁴⁷) and associated with other cardiometabolic (e.g., *HTR1A*⁴⁸, *PSRC1*⁴⁹,

*PSKHI*⁵⁰), inflammatory (e.g., *IL33*⁵¹), cognition (e.g., *FRMD4A*⁵²) and psychiatric traits (e.g., *NFATC3*⁵³) (Supplementary Tables 26 and 27).

In total, 11 novel loci harbored genes implicated in Mendelian syndromes such as ventricular tachycardia and cryptogenic cirrhosis. 13 loci harbored one or more genes with potential drug targets (Supplementary Tables 26 and 27).

We performed tissue and pathway enrichment analyses using annotated genes under novel association regions using FUMA³⁶ (Supplementary Tables 28 and 29). Genes under the association regions in gene-LTST interaction analyses were enriched in multiple artery and cardiac muscle related pathways (Supplementary Table 30).

Discussion

We performed genome-wide gene-sleep interaction analyses on BP using 122,265 individuals from 5 ancestry groups in 30 studies in two stages, using a 2df joint test of main and interaction effects followed 1df test investigation of interaction effects. Primary 2df GWIS in multi-ancestry group identified 3 novel loci that were replicated in additional samples (stage 1+2 $P_{\text{joint}} < 5 \times 10^{-8}$). Secondary ancestry specific 2df GWIS additionally identified 3 novel loci with weak replication evidence in AFR. Combined stage 1 and 2 analyses identified another 20 novel loci after accounting for multiple comparisons ($P_{\text{joint}} < 3.125 \times 10^{-9}$), which require external replication. The associations were largely unchanged after additionally adjusting for BMI.

The emergence of novel loci after considering gene-sleep interactions suggests an important modifying role of sleep on BP regulation, which involves both central and peripheral regulation (including the brain, adrenal glands, kidneys, and vasculature). Insufficient or short sleep can increase BP through effects on elevating sympathetic nervous system activity and

altering hypothalamic-pituitary-adrenal (HPA) axis activities, leading to hormonal changes, endothelial dysfunction, insulin resistance, and systemic inflammation^{19, 54}. The mechanisms underlying the association between long sleep duration and BP are less well understood, and may reflect circadian misalignment in a 24-hour period, including disrupted sleep-wake cycle, a misalignment of internal biological clocks with the external environment, and desynchronized central and peripheral clocks in tissues relevant for BP control⁵⁵. The importance of circadian control of BP is evident by the normal nocturnal decline (“dipping”) in BP. Non-dipping of BP, associated with increased mortality, is observed with both sleep disturbances and abnormalities of sodium transport in the kidney^{56, 57}. Our data suggest that sleep and renal and neuro-endocrine control of BP may interact to influence susceptibility to HTN. The novel loci found by gene-LTST and gene-STST interaction analyses were distinct, supporting the different mechanisms of short and long sleep modifying BP. Similarly, in prior gene-sleep interaction analyses for blood lipids, LTST and STST each also modified gene effects in a non-overlapping pattern¹⁸.

Using the 1df test, we identified three novel gene-sleep interactions that were formally replicated in primary multi-ancestry analyses (stage 1+2 $P_{\text{int}} < 5 \times 10^{-8}$). Among those, rs7955964 (*FIGNL2/ANKRD33*) only increased MAP in long sleepers (Fig 2A). In the association region under this locus, *ANKRD33* is expressed in retinal photoreceptors and the pineal gland and acts as a transcriptional repressor for CRX-activated photoreceptor gene regulation³⁸. Given the importance of light in the central regulation of circadian rhythms, long sleep- a circadian disruptor- may interact with this gene to influence BP⁵⁶. Additionally, *NR4A1* (that also maps to this locus) is a member of the nuclear hormone receptor family, which regulate neurohormonal systems including dopamine and norepinephrine and cardiac stress responses^{39, 58}. Its expression is influenced by an array of stimuli, including those influence nutrient sensing. Our findings

suggest that perturbed sleep and circadian rhythms may also alter the effects of this gene, increasing BP.

Rs10406644 (*KCTD15/LSMI4A*) only increased PP in short sleepers. *KCTD15* is implicated in both renal (nephron) development and adiposity, possibly through effects on Wnt signaling and neural crest development. Short sleep can lead to hypothalamic-adrenal-cortisol dysfunction, and potentially may amplify the effects of this gene on metabolism and kidney function to increase BP^{59, 60}. This locus also maps to *CHST8* that is associated with adiposity traits^{40, 41} as well as to *GPI* that functions in glucose metabolism and immune system pathways^{61, 62}.

Rs73493041 (*SNORA26/C9orf170*) only increased DBP in short sleepers. Rs73493041 was an eQTL for *GAS1*, a pleiotropic regulator of cellular homeostasis and widely expressed in the central nervous system^{63, 64}. The risk allele was also significantly associated with self-reported eveningness chronotype ($P=9.1 \times 10^{-6}$; Supplementary Table 22), a circadian phenotype associated with increased cardiometabolic and neuropsychiatric disorders⁶⁵. Short sleep may magnify cardiometabolic dysfunction associated with delayed sleep timing.

Given the high prevalence of HTN in African Americans, there is a critical need to identify modifiable risk factors. Notably, African Americans have poorly controlled HTN as well as circadian abnormalities in BP regulation⁶⁶. They also have a higher prevalence of short and long sleep duration compared to individuals of European ancestry^{67, 68}, likely due to combinations of social-environmental exposures and genetic and epigenetic susceptibility⁶⁹. In AFR specific gene-LTST analyses, we identified a novel SNP-LTST interaction at rs111887471 (*TRPC3/KIAA1109*) with risk effect on SBP only present in long sleepers ($P_{\text{int}}=2 \times 10^{-6}$; Supplementary Fig. 14). *TRPC3* has been shown to play an important role in cardiac ion (Na^+

and Ca^{2+}) homeostasis⁴³. The association observed in in AFR may reflect differences in BP control with individuals of African ancestry having greater sodium sensitivity⁷⁰, with BP effects amplified by disrupted circadian rhythm regulation due to long sleep⁵⁷.

Combined stage 1 and 2 analyses additionally identified significant gene-LTST interactions at *MKLN1*, *RGL3/ELAVL3*, *LINC01720/AL138927.1*, *RYR2*, *SEMA4F/HK2*, *DPP10/DDX18*, *PDZRN3/CNTN3*, *LEKR1/LINC00880*, *FSTL5*, *AC008558.1/HTR1A*, *ZFPM2* and significant gene-STST interactions at *C2orf43*, *GJA4*, *PSRC1/MYBPHL*, *AL033381.3/FOXQ1*, *PTPRN2*, *ERICH1*, *AL162384.1/IL33*, *FRMD4A*, *RP11-408B11.2*, and *TTC6* ($P_{\text{int}} < 10^{-3}$), which require external replication. *MKLN1*, *RGL3/ELAVL3*, and *C2orf43* has been reported associated with BP previously. Among those, *MKLN1* regulates the internalization and transport of the GABA_A receptor^{71, 72} and *ELAVL3* encodes a neural-specific RNA-binding protein involved in neuronal differentiation and maintenance⁷³. We did not observe marginal main effects for those loci among normal sleepers (Supplementary Fig. 14), perhaps because of the small sample size of those variants ($N \leq 10,038$; Supplementary Table 10). Our findings suggest that their effects on BP may be amplified in the setting of long sleep due to disrupted circadian rhythm regulation when these effects were not detectable in small samples.

In this study we defined short and long sleep duration using self-reported questionnaires, which can result in misclassification⁷⁴, potentially reducing statistical power. Although we used a within cohort approach for harmonizing sleep duration that accounted for age and sex differences across cohorts, there may be systematic residual differences in sleep assessments that resulted in heterogeneity across our samples. Future work using objective measurements (e.g., polysomnography and actigraphy data) may provide further insight into sleep-related BP mechanisms.

Some of our most interesting findings - and ones with high potential public health impact due to the burden of extreme sleep duration and HTN in AFR group. Unfortunately, limited samples of AFR were available for replication. We identified 1,976 variants with significant association effect in gene-sleep interaction analyses in stage 1. However, only 1,081 of those variants were available in stage 2 analyses. Most of the unavailable variants in stage 2 had been identified in non-EUR cohorts and were rare in EUR populations (MAF<1%). Future studies following-up these “missing” variants in diverse groups and additional studies of minority populations are needed to further understand mechanisms for BP regulation that are modulated by sleep. In addition, some of our findings were mapped to large genomic regions covering many genes. Further fine-mapping analyses using sequencing data or biochemistry experiments may further clarify the causal variants.

In summary, we performed a large-scale gene-sleep interaction meta-analyses in multi-ancestry groups. This study advances our knowledge on the interactions between genetic risk factors, sleep duration and blood pressure. This work extends prior research that has reported that extreme sleep durations (short or long) are associated with increased blood pressure as well as cardiovascular morbidity¹⁹, and provides evidence that sleep duration may modify genetic risk for hypertension through pathways that influence photoreception, metabolism, adiposity, renal function, and chronotype. These findings also suggest that sleep duration may modify the effects of antihypertensives that target certain genes or pathways—an area that should be further investigated using pharmacogenetics and pathway-level approaches. Finally, the observation of multiple genetic effects only in individuals with extreme sleep duration supports the general guidance for the public to follow published sleep duration recommendations (7-9 hours) ⁷⁵ –

568 potentially reducing cardiovascular diseases in the population, especially for individuals with
569 genetic predispositions.

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Author contributions:

H.W., B.E.C., and J.L. conducted the centralized data analyses, including quality controls, meta-analyses, and post association lookups and bioinformatics. H.W., R.N., B.E.C., K.S., T.W.W., J.L., Y.J.S., A.R.B., D.C.R., S.R. and D.v.H. were part of the writing group and participated in study design, interpreting the data, and drafting the manuscript. All other co-authors were responsible for cohort-level data collection, cohort-level data analysis and critical reviews of the draft paper. All authors approved the final version of the paper that was submitted to the journal.

Conflict of Interest

D.O.M.K. is a part time research consultant at Metabolon, Inc. B.M.P. serves on the DSMB of a clinical trial funded by the manufacturer (Zoll LifeCor) and on the Steering Committee of the Yale Open Data Access Project funded by Johnson & Johnson. H.J.G. has received travel grants and speakers honoraria from Fresenius Medical Care, Neuraxpharm, Servier and Janssen Cilag as well as research funding from Fresenius Medical Care. The remaining authors declare no competing interests.

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873 **Figure legends**

874 **Fig. 1.** Study overview.

875 **Fig. 2.** Forest plots of effects on BP in long, normal, and short sleepers at 3 replicated novel loci
876 in the multi-ancestry population.

877

Table 1. Replicated novel BP loci significantly associated with sleep duration.

Exposure	rsID	Gene(s)	Chr: position (Build 37)	Alleles (E/A)	EAF	Trait	Stage	BMI adjustment	N	β_{SNP}	SE _{SNP}	β_{Int}	SE _{Int}	P _{Joint}	P _{Int}
LTST	rs7955964	<i>FIGNL2, ANKRD33</i>	12:52281279	A/T	0.896	MAP	1	Without BMI	18583	-0.400	0.290	2.711	0.582	1.75×10 ⁻⁶	1.34×10 ⁻⁶
								with BMI	18583	-0.462	0.279	2.768	0.546	2.48×10 ⁻⁷	2.10×10 ⁻⁷
							2	Without BMI	12335	-0.621	0.289	2.163	0.632	2.52×10 ⁻³	5.49×10 ⁻⁴
								with BMI	12327	-0.519	0.281	2.210	0.613	1.72×10 ⁻³	2.66×10 ⁻⁴
							1+2	Without BMI	29985	-0.517	0.208	2.505	0.433	1.11×10 ⁻⁷	4.40×10 ⁻⁹
								with BMI	29957	-0.500	0.201	2.577	0.413	6.74×10 ⁻⁹	2.94×10 ⁻¹⁰
STST	rs73493041	<i>SNORA26, C9orf170</i>	9:89849304	T/C	0.959	DBP	1	Without BMI	36858	-0.725	0.229	2.336	0.471	4.65×10 ⁻⁷	3.6×10 ⁻⁷
								with BMI	36858	-0.723	0.219	2.235	0.456	5.16×10 ⁻⁷	5.18×10 ⁻⁷
							2	Without BMI	24413	-0.763	0.321	1.888	0.705	5.44×10 ⁻³	9.43×10 ⁻³
								with BMI	24385	-0.704	0.335	1.875	0.704	1.09×10 ⁻²	1.27×10 ⁻²
							1+2	Without BMI	61271	-0.724	0.185	2.213	0.387	3.62×10 ⁻⁸	1.30×10 ⁻⁸
								with BMI	61243	-0.709	0.182	2.132	0.381	7.15×10 ⁻⁸	2.58×10 ⁻⁸
	rs10406644	<i>KCTD15, LSM14A</i>	19:34595645	A/G	0.095	PP	1	Without BMI	15021	0.542	0.275	-3.194	0.605	1.26×10 ⁻⁷	1.35×10 ⁻⁷
								with BMI	12921	0.565	0.306	-3.382	0.677	5.23×10 ⁻⁷	4.81×10 ⁻⁷
							2	Without BMI	11401	1.142	0.587	-2.702	1.163	4.59×10 ⁻²	2.02×10 ⁻²
								with BMI	11373	1.102	0.582	-2.533	1.155	6.08×10 ⁻²	2.83×10 ⁻²
							1+2	Without BMI	26422	0.648	0.249	-3.067	0.536	1.39×10 ⁻⁸	7.59×10 ⁻⁹
								with BMI	24294	0.678	0.271	-3.135	0.584	8.56×10 ⁻⁸	4.35×10 ⁻⁸